Advisory Committee for Pharmaceutical Science (ACPS)
Nonclinical Studies Subcommittee Meeting (NCSS)
November 13, 2001
FDA Building 5630

ACPS Participants:
John Doull, M.D., Ph.D. - Chair
University of Kansas Medical Center
Gloria Anderson, Ph.D. - Consumer Rep.
Morris Brown College

Consultants & Experts:
Joy Cavagnaro, Ph.D.

Industry Participants:
Jack H. Dean, Ph.D., D.A.B.T.
Sanofi-Synthelabo
Jack A Reynolds, D.V.M.
Pfizer, Inc.

Industry Invited Guest:
Gordon Holt, Ph.D.
Oxford GlycoSciences

Acting Executive Secretary
Kimberly L. Topper, MS

Academic Participants:
Kendall B. Wallace, Ph.D., D.A.B.T.
University of Minnesota

Government Participants:
David M. Essayan, M.D. - CBER
James T. MacGregor - NCTR
Helen N. Winkle - CDER
Thomas Papoian, Ph.D. - CDER
Elizabeth A. Hausner, D.V.M., D.A.V.T. - CDER

I certify that I attended the November 13, 2001 meeting of the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science and that these minutes accurately reflect what transpired.

Kimberly L. Topper, MS Acting Executive Secretary, NCSS	Date	John Doull, M.D., Ph.D. Chair, NCSS	Date

A verbatim transcript of this meeting is available for more detailed information.

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The meeting was called to order at 8:05 and Dr. Doull welcomed the group and covered the goals of the meeting. The Conflict of Interest statement was read into the record. The committee, guests, and experts introduced themselves.

Dr. Wallace presented the report of the Cardiotoxicity Biomarker Expert Working Group (CBEWG). He covered the progress since the last report to the committee and the near future plans.

Progress since last report to the NCSS July 2001:

The CBEWG met in Rockville, MD on Oct 12, 2001 to discuss evidence regarding the troponins and to plan objectives and logistics for College of Toxicology symposium.

The CBEWG met November 6 at the Renaissance Hotel:

- Morning CBEWG meeting to finalize criteria of an "ideal" biomarker of drug-induced cardiotoxicity and to establish objectives and plans for the symposium.
- Afternoon symposium with open discussion and solicitation of input from the audience regarding troponins as biomarkers of drug-induced cardiotoxicity.
- Evening CBEWG meeting to agree on conclusions from symposium and decide next steps.

Near future plans:

- The CBEWG is currently drafting a position paper regarding the use of cardiac troponins T and/or I as biomarkers of drug-induced cardiac injury, wherein a treatment-associated increase in circulating troponin should be considered an indication of treatment-related myocardial cell injury.
- The CBEWG is currently drafting the design of a definitive experiment to determine whether a quantitative correlation exists between the magnitude of increase in circulating troponin and the extent of cardiac histopathology.
- The CBEWG is currently gathering and evaluating evidence regarding other small molecules and proteins that have been suggested to reflect drug induced or ischemia-related cardiac injury.

The committee discussed all of the issues addressed and the following are the main concerns:

- The information should be published but should be published within the FDA rules for publishing data because these findings will have a far-reaching effect.
- This CBEWG should continue to look forward and consider getting data that is within industry to use in their evaluation of troponin as a biomarker in early development.
- The CBEWG should be clear in providing the data to indicate troponin's are excellent biomarkers in animal models.
- The CBEWG should consider if the marker is a bridging biomarker from animals to humans.

The committee asked the CBEWG to consider:

- Publication of the data used to come to the conclusions.
- Bring back issues, as they are developed to get committee input.
- ICVAM Model of research

Dr. Papoian presented the report of the Vasculitis Expert Working Group. The EWG name was changed to Vascular Injury Expert Working Group (VIEWG) because the terminology of the mechanism of injuring event vs repair and inflammatory responses that follow will influence selection of potential markers. He discussed budget issues and the groups they propose to contact for funds.

The Goals of the VIEWG are to explore mechanistic biomarkers, explore targeted late stage biomarkers, and support broad exploration via genomics, proteomics, and metabonomics.

The potential biomarker targets are:

- Injury phase
  - Aptosis markers
  - Circulating endothelial cells (CD31 or Annexin)
- Inflammatory Phase
  - Cytokines
  - Acute Phase Proteins (a2, haptoglobin, CRP)
- Fishing Expedition
  - Gene expression mapping. Endothelial cells and vascular smooth muscle cells.
  - Urinary or plasma NMR spectra
  - Proteomics

The next steps the VIEWG will take are to continue the independent research, define a standard model for testing, establish cooperative analytical effort to support centralized animal studies and consider inviting other stakeholders to participate in the studies.

The committee discussed the report and had the following concerns:

- Recommend a veterinary immunopathologist should be on the VIEWG to address species specific issues.
- A workshop would be a good way to get all parties to the table for discussions.
- Funding is an issue and all the rules and regulations must be reviewed before funding is appropriated.

Dr. MacGregor and Ms. Helen Winkle presented information on moving the NCSS from ACPS to National Center for Toxicological Research (NCTR). They explained that CDER's mission is focused on review and ensuring the drugs on the market are safe and effective and the NCTR's main focus is research and they are funded to do the research. The NCSS would report to the NCTR Science Board instead of the ACPS. Ms. Winkle recommended that there would still be ACPS members sitting on the NCSS, there would be joint meetings of the NCTR Science Board and the ACPS, and there would still be members of CDER working with the EWG's. She stated that CDER ACPS wants to and plans to stay active within NCSS.

Dr. Joe DeGeorge stated that a cross center dialog is a critical concern when considering the move to NCTR but with other issues there has been a good relationship between NCTR and CDER.

The committee had the following concerns:

- The NCSS and EWG's would have to compete with other research projects within NCTR funds and wanted to ensure the Science Board would not say "No" to the projects they have already started.
- The NCSS and EWG's wanted to ensure they continued to get the scientific input and member support they were receiving from CDER.
- The NCSS and EWG's were concerned about funding and which committee would be their parent committee.

After much discussion Dr. MacGregor and Ms. Winkle will continue the dialog and review all of the concerns expressed by NCSS and bring the issue back at a later date.

There were no advance requests for time at the Open Public Hearing and the audience was invited to make comments and no one accepted the opportunity.

The meeting was adjourned at 11:50 am.